New Drug Targets for Diabetes

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Objectives

- To describe glucose homeostasis
- To describe the incretin system
- To describe new treatment options in diabetes
- To describe the FDA approval process for new medications and indications

medications

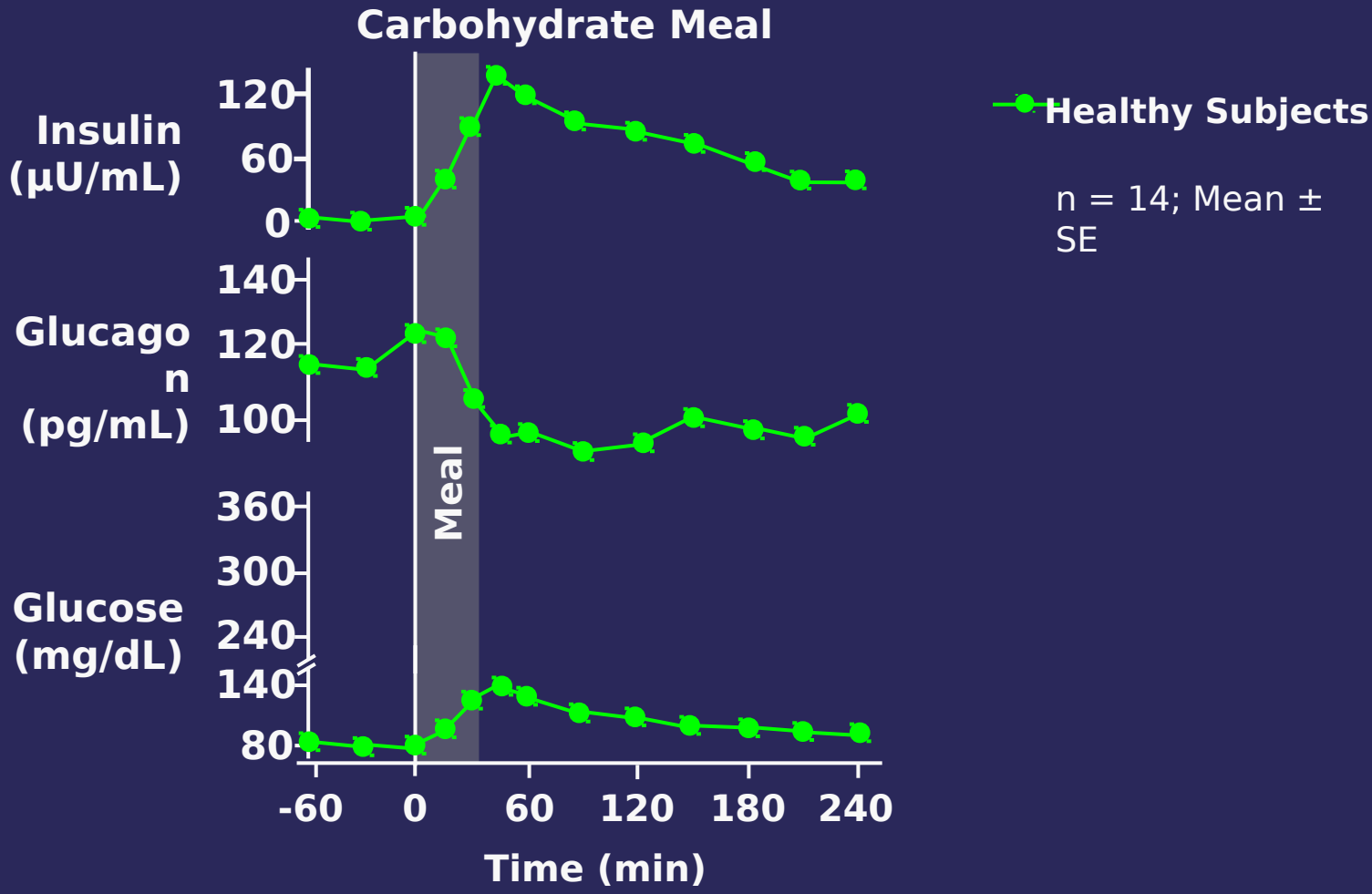
Medications	Introduction or FDA approval
Insulin	1921
Inhaled insulin	2006
Sulfonylureas	1946
Biguanides	1957 (metformin 1995)
Glycosidase inhibitors	1995
TZDs Troglitazone Pioglitazone Rosiglitazone	 1997 1999 1999
Meglitinides	1997
GLP analogues	2005
Amylin analogues	2005
DPP-IV inhibitors	2006

New Drug Targets

- Incretins
  - GLP1 analogues: Exenatide (Byetta)
  - DPP4 Inhibitors: Sitagliptin (Januvia)
- Amylin
  - Pramlintide (Symlin)
- Inhaled insulin (Exubera)

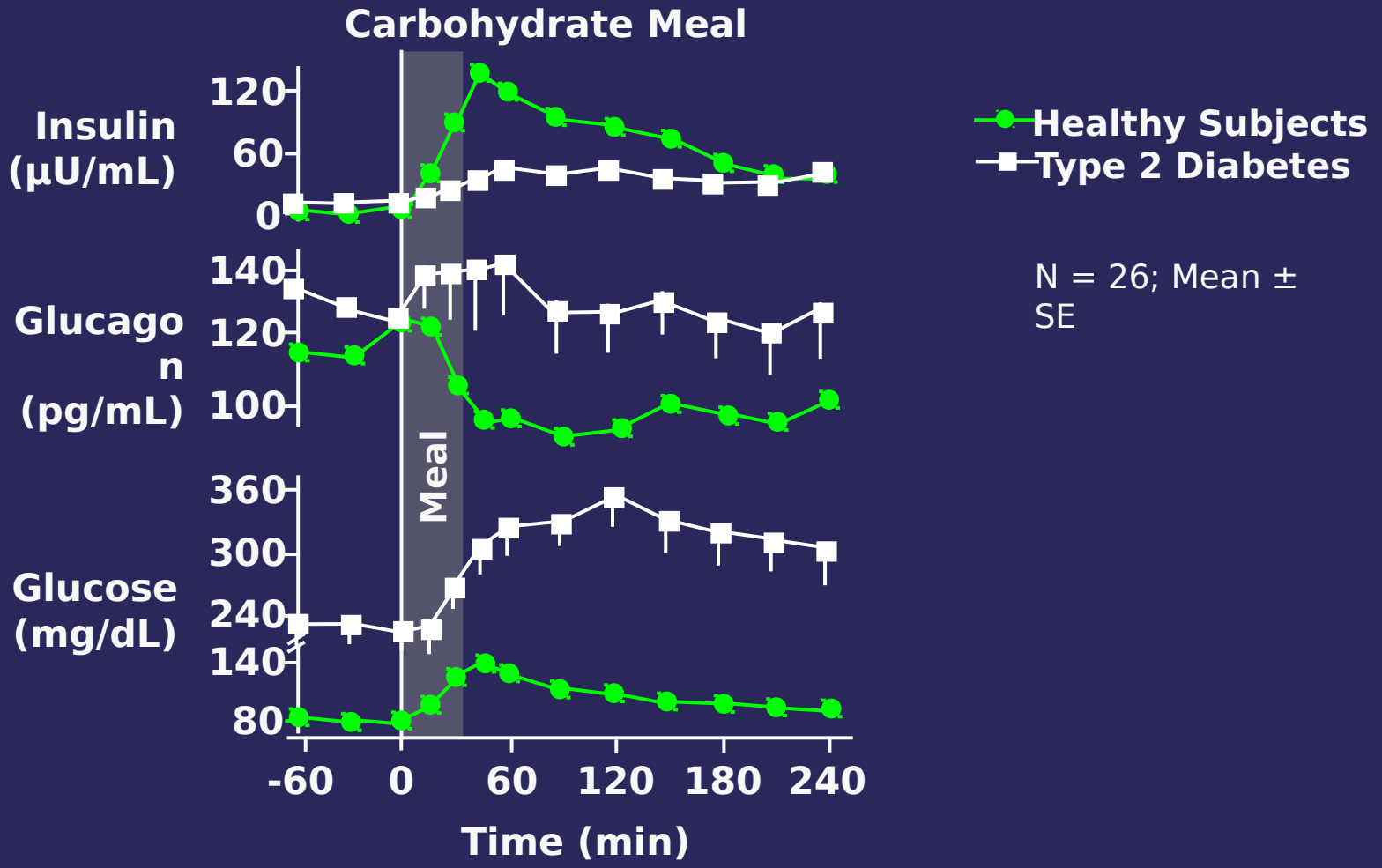
GLUCOSE HOMEOSTASIS and the Incretin system

β-Cell Workload in Healthy Subjects



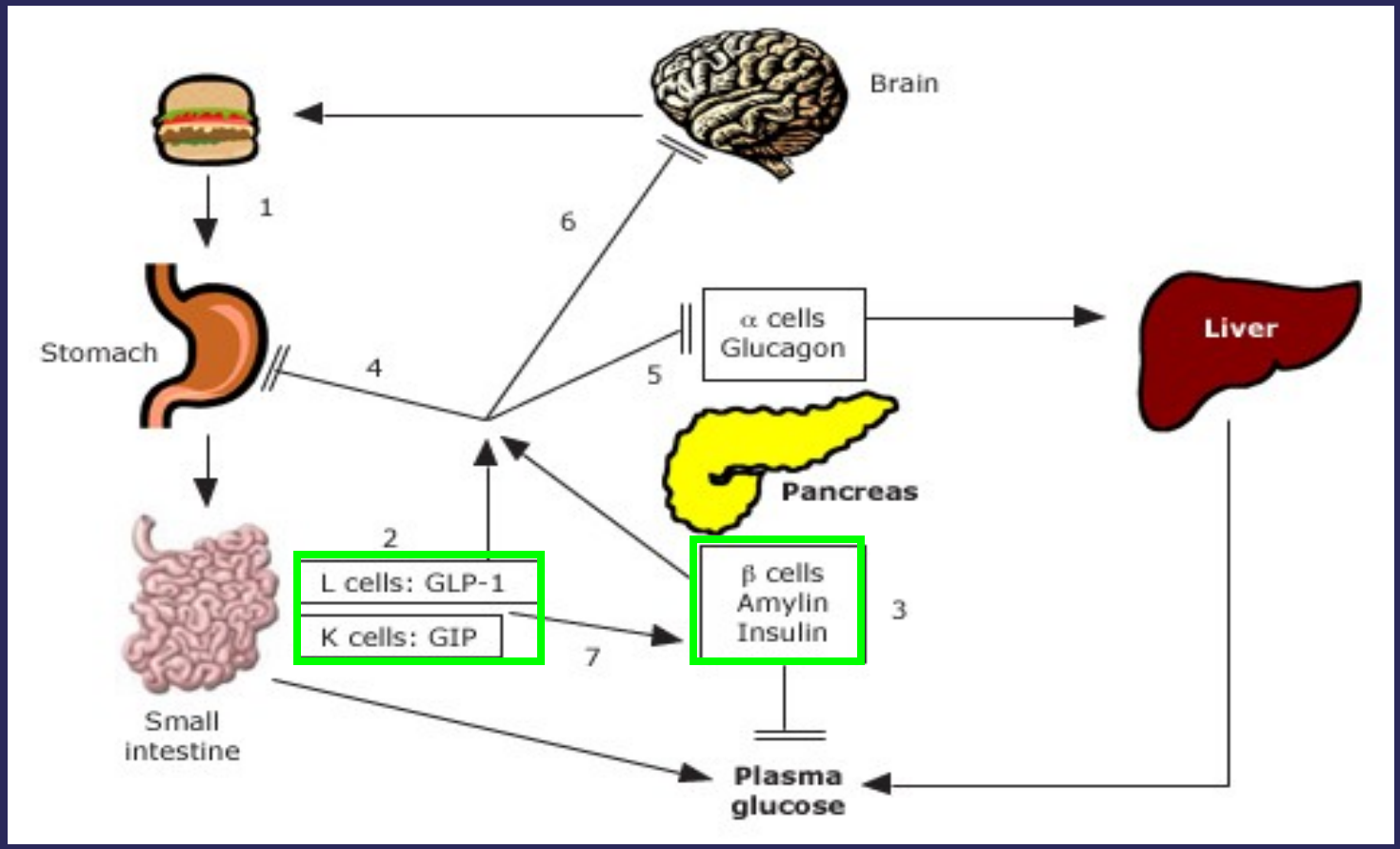
Müller WA, et al. N Engl J Med. 1970;283:109-115.

β-Cell Workload in Type 2 Diabetes



Müller WA, et al. N Engl J Med. 1970;283:109-115.

Multinational Regulation of Glucose Homeostasis



Dungan K, Buse JB. Amylin and GLP-1-based therapies for the treatment of diabetes. UpToDate 2006. Available at www.uptodate.com. Accessed December 24, 2006.

Role of Incretin in Glucose Homeostasis

IN-CRET-IN

INtestine seCRETion INsulin

Definition: gut derived factors that increase glucose stimulated insulin secretion

Two hormones: (1) glucagon-like peptide-1 (GLP-1)

(2) glucose-dependent insulinotropic polypeptide (GIP)

Creutzfeldt Diabetologia 28: 5645 1985

GLP-1 and GIP Are Incretin Hormones

GLP-1

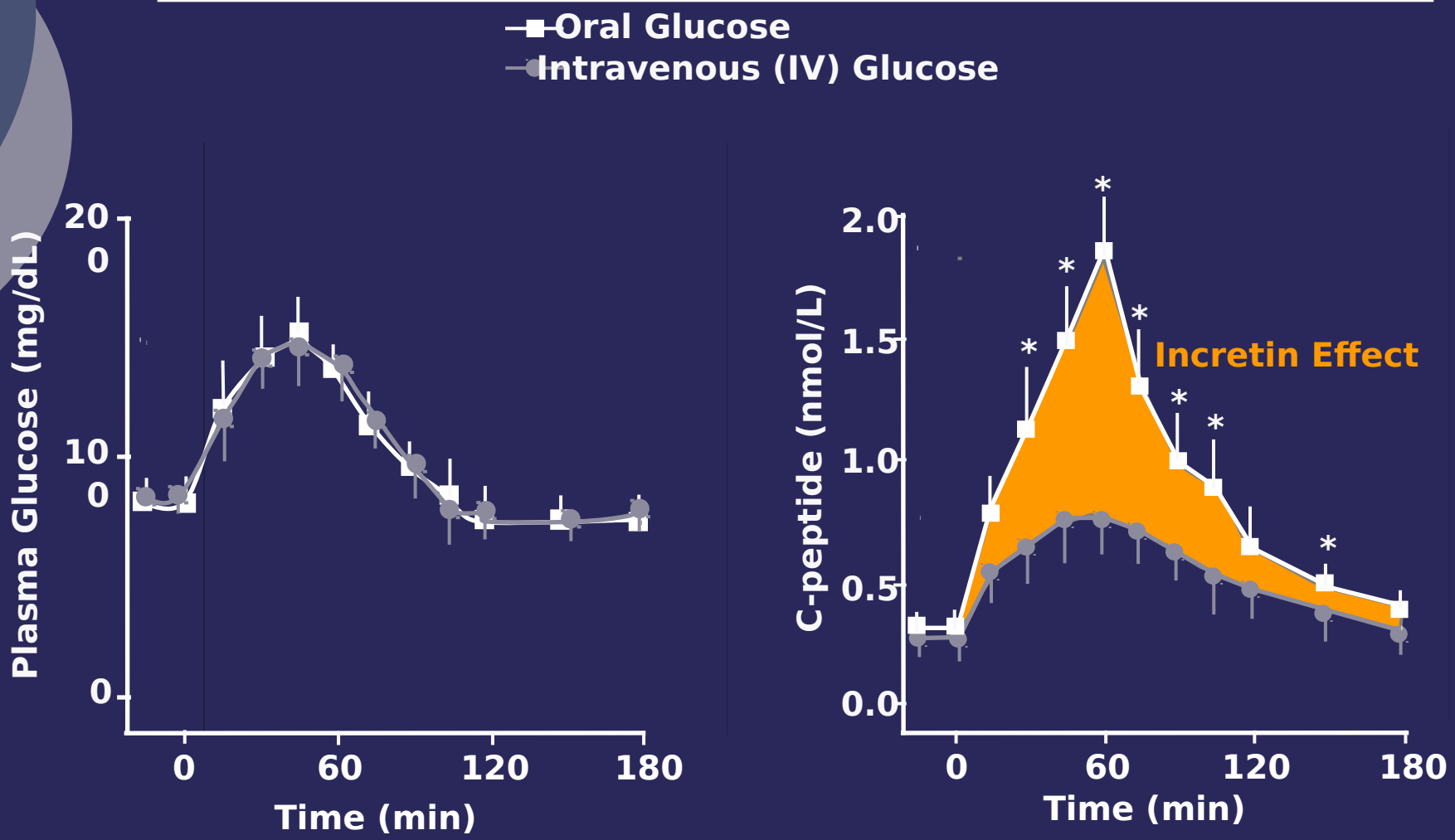
- **Released from L cells in ileum and colon[1,2]**
- **Stimulates insulin from beta cells in a glucose-dependent manner[1]**
- **Inhibits gastric emptying[1,2]**
- **Reduces food intake and body weight[2]**
- **Inhibits glucagon secretion from alpha cells in a glucose-dependent manner[1]**
- **Deficient in type 2 diabetes**

GIP

- **Released from K cells in duodenum[1,2]**
- **Stimulates insulin from beta cells in a glucose-dependent manner[1]**
- **Minimal effects on gastric emptying[2]**
- **No significant effects on satiety or body weight[2]**
- **Does not appear to inhibit glucagon secretion from alpha cells[1,2]**
- **Normal levels but decreased responsiveness in type 2 diabetes**

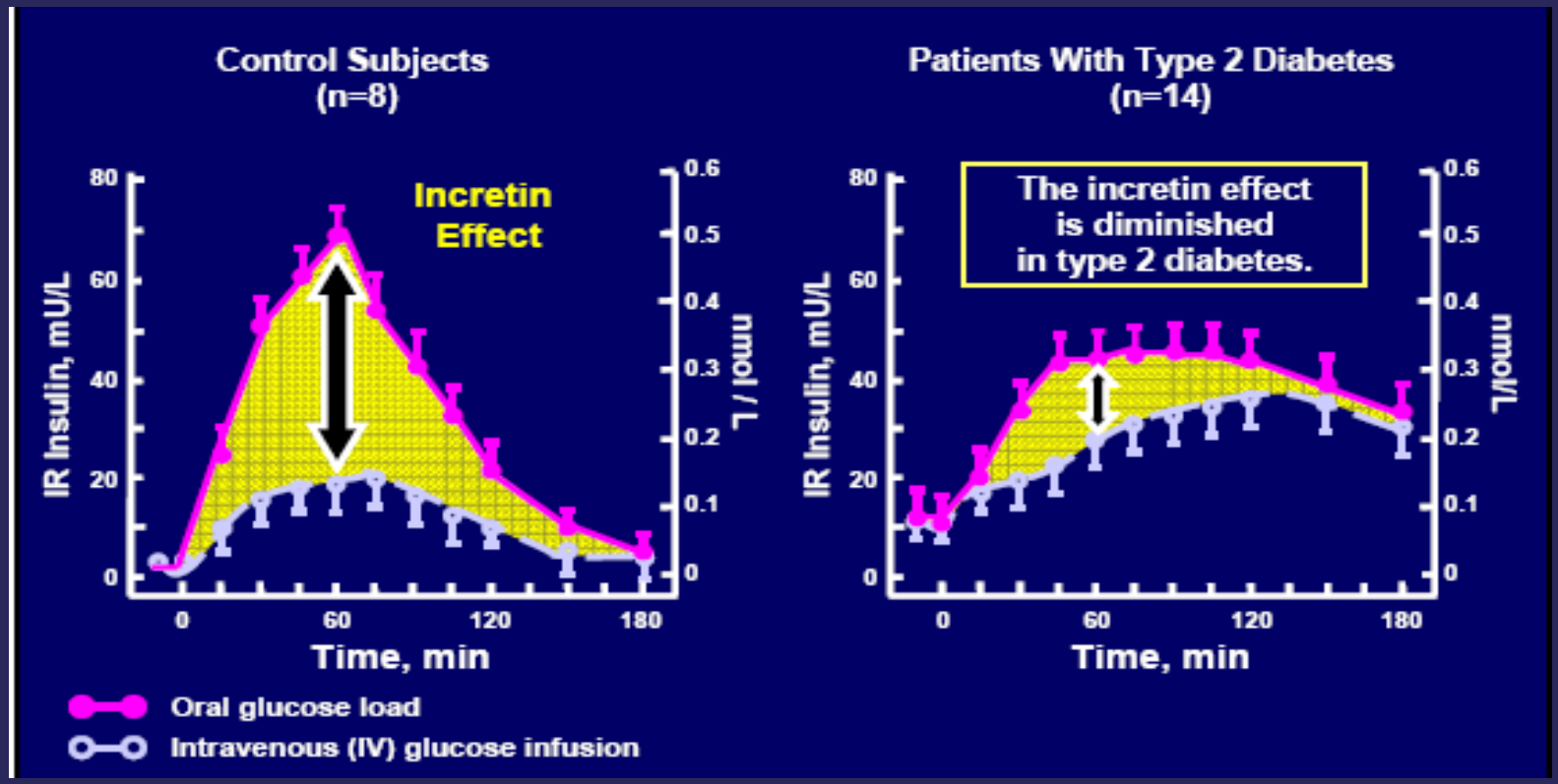
1. Meier JJ et al. *Best Pract Res Clin Endocrinol Metab*. 2004;18:587–606.
2. Drucker DJ. *Diabetes Care*. 2003;26:2929–2940.

The Incretin Effect in Healthy Subjects



N = 6; Mean ± SE; *P≤0.05
Nauck MA, et al. J Clin Endocrinol Metab. 1986;63:492-498.

Loss of Incretin Effect



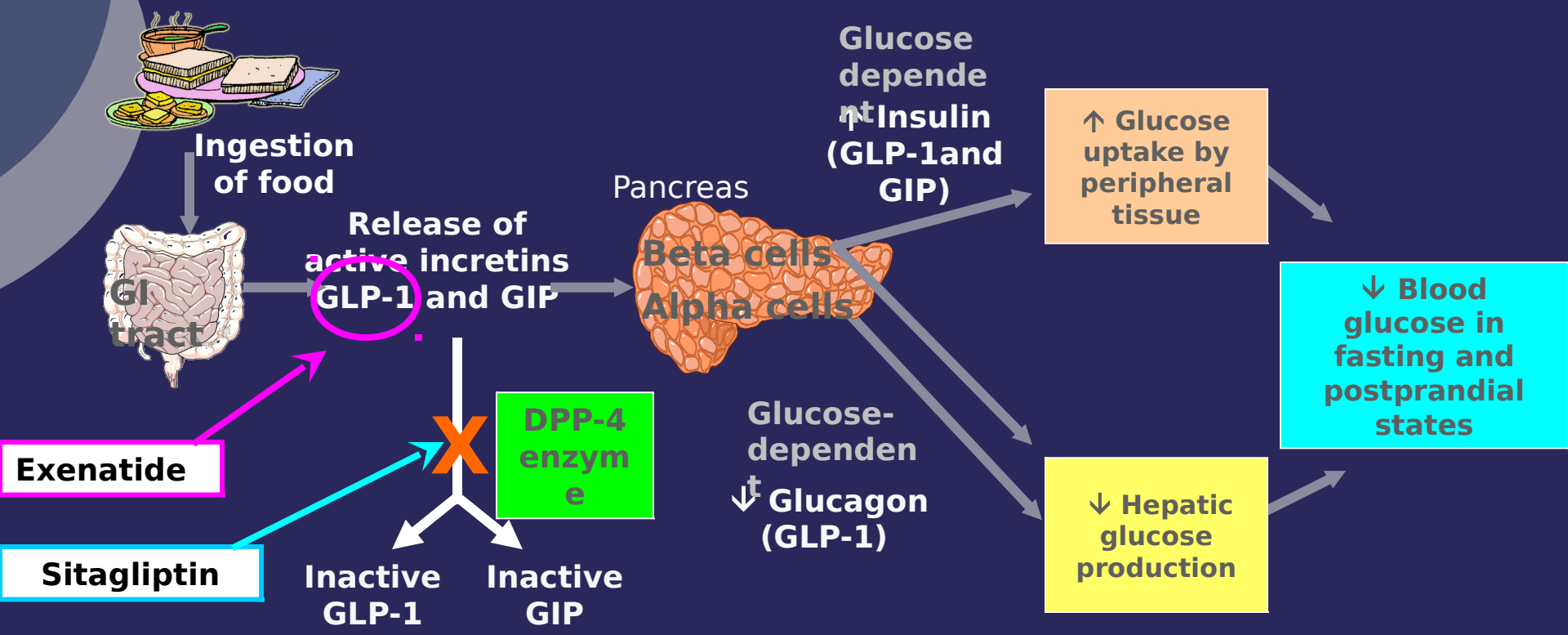
Nauck M,et al. Diabetologia 1986;29:46-52.

Incretins: The medications

GLP1 analogues:Exenatide (Byetta)

DPP4 Inhibitors:Sitagliptin (Januvia)

New Therapies: Incretin System



GLP-1=glucagon-like peptide-1; GIP=glucose-dependent insulinotropic polypeptide.

DPP-4 Inhibitors and Incretin Mimetics

	Sitagliptin (Januvia®)	Exenatide (Byetta®)
Indication	Management of type 2 diabetes mellitus - monotherapy - combo with metformin or TZD	Management (adjunctive) of type 2 diabetes mellitus - metformin, sulfonylurea, and/or TZD
Dose	○100mg daily ○CrCl ≥ 30 to < 50ml/min: 50mg/day ○CrCl < 30ml/min or with ESRD requiring dialysis: 25mg/day ○Route: oral	○Initial: 5mcg bid within 60 minutes prior to a meal (morning and evening) ○After 1 month, may be increased to 10mcg bid ○CrCl < 30ml/min: not recommended ○Route: SC

Sitagliptin prescribing information, 2006. Exenatide prescribing information, 2007.

DPP-4 Inhibitors and Incretin Mimetics

	Sitagliptin (Januvia®)	Exenatide (Byetta®)
Adverse Reactions	○Monotherapy: nasopharyngitis ○Combination with TZDs: upper respiratory tract infxn, headache ○GI: abdominal pain, N/V/D	○Monotherapy: N/V/D ○Combination with sulfonylurea: hypoglycemia ○Anti-exenatide antibodies ○Weight loss • Long-term unclear
Comments	○ Should NOT be used in type 1 diabetes or for treatment of diabetic ketoacidosis	

Sitagliptin prescribing information, 2006. Exenatide prescribing information, 2007.

Comparison: DPP-4 Inhibitors and Incretin Mimetics

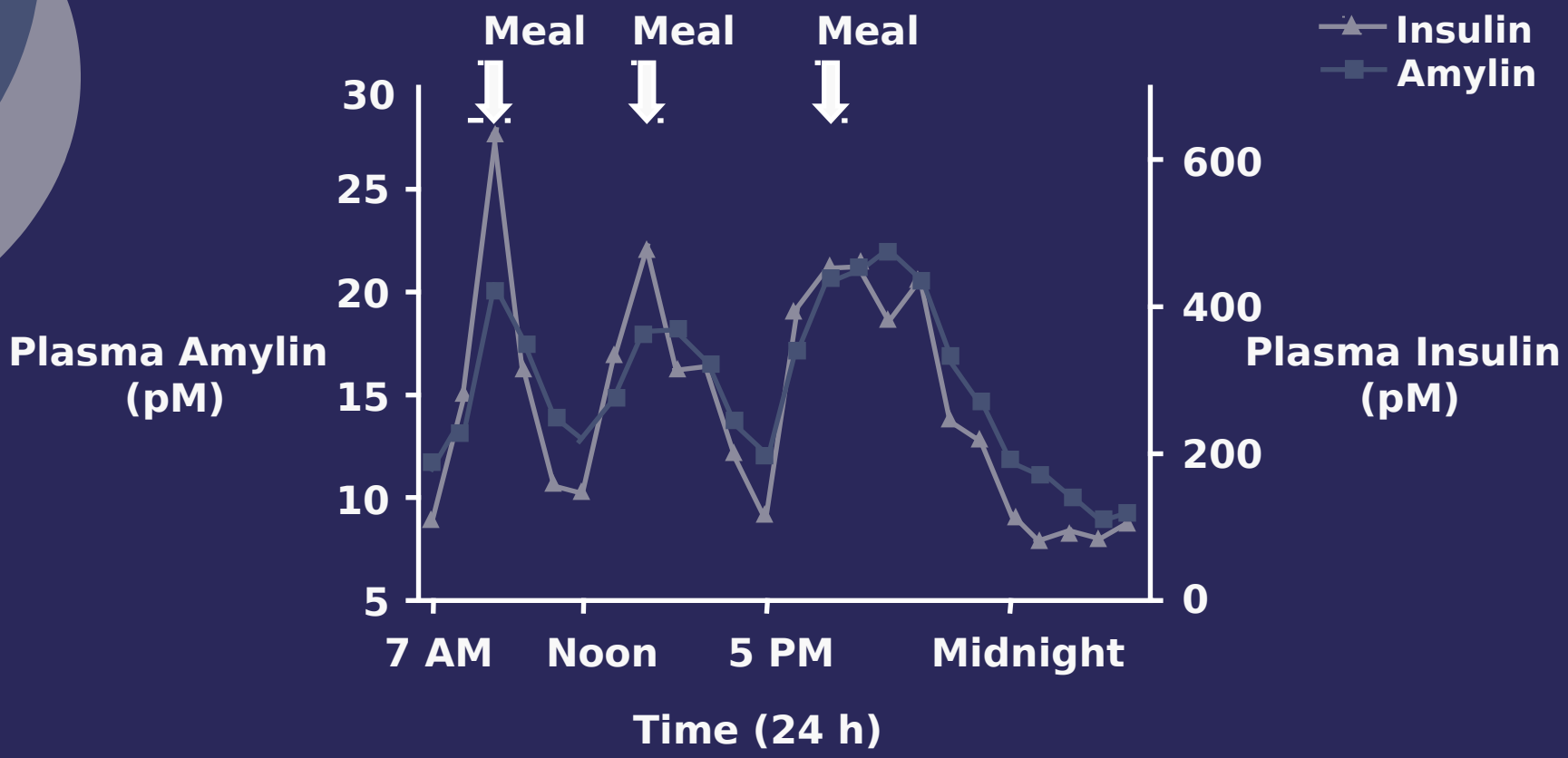
	DPP-4 Inhibitors (Sitagliptin)	Incretin Mimetics (Exenatide)
Advantages	○ Route: oral ○ No weight gain ○ Promote b-cell proliferation ○ Once daily dosing	○ Weight loss independent of nausea ○ Promote b-cell proliferation and islet neogenesis ○ Induces satiety, suppresses appetite
Disadvantages	○Unwanted effects on immune function (possible safety issues) ○Less potent compared with injectable incretin mimetics	○ Route: SC ○ Twice daily dosing ○ Dose-dependent nausea and vomiting ○Fixed dosing (Pen)

(1) Nauck M, et al. Diabetologia 1986;29:46-52. (2) Triplitt C, et al. Pharmacotherapy 2006;26:360-374. (3) Drucker D, et al. Lancet 2006;368:1696-1705

Amylin the Hormone

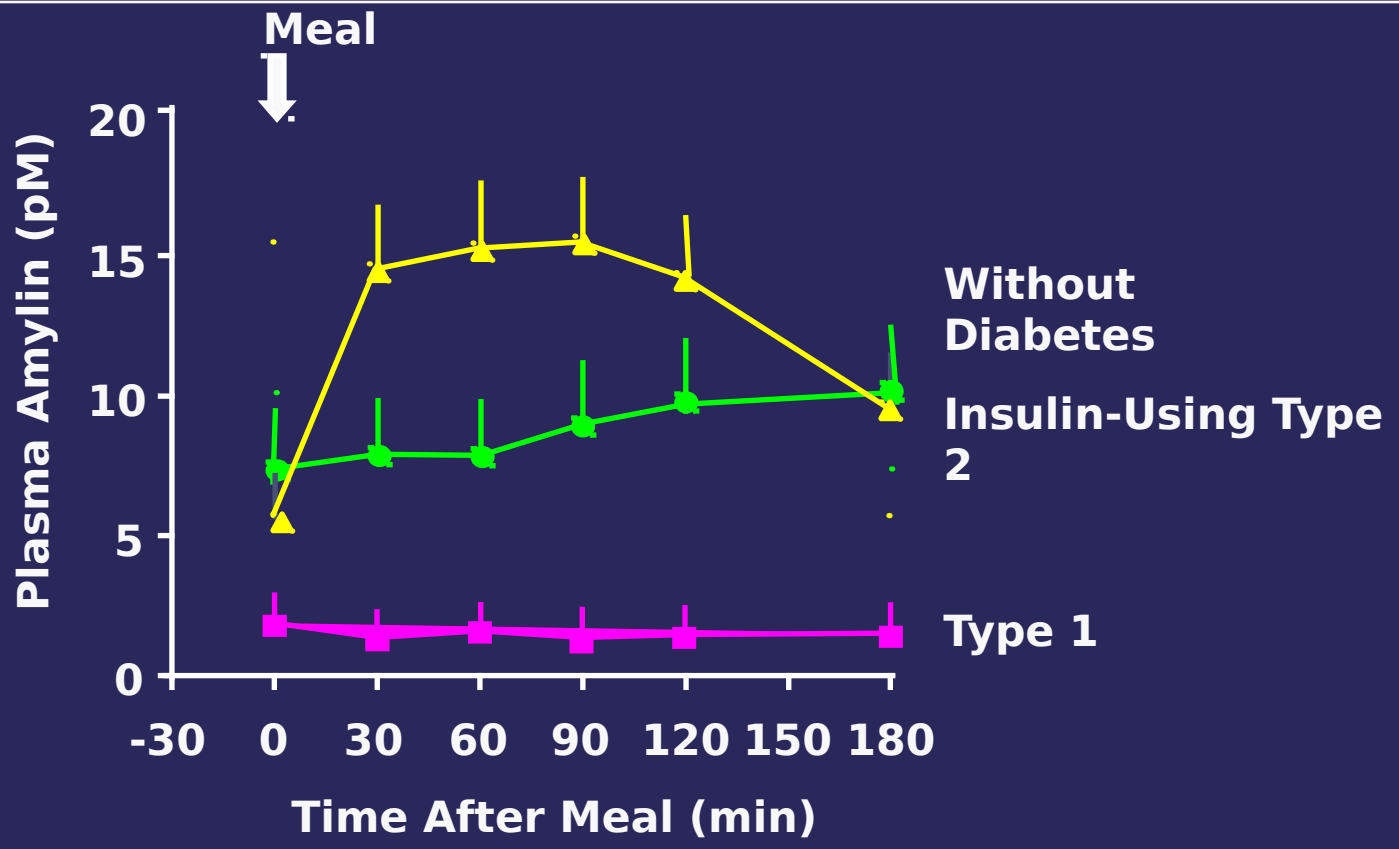
- Reported in 1987
- 37-amino acid peptide
- Neuroendocrine hormone

Amylin: Co-Secreted With Insulin



Healthy subjects, n = 6; Mean
Data from Kruger D, et al. *Diabetes Educ* 1999; 25:389-398

Amylin: Deficient in Diabetes



Without diabetes, n = 27

Insulin-using type 2, n = 12

Type 1, n = 190; Mean data

Kruger D, et al. *Diabetes Educ* 1999; 25:389-398

Amylin: Mechanism of Action

- Inhibits inappropriately high postprandial glucagon secretion
- Slows gastric emptying
- Promotes satiety and reduces caloric intake

Pramlintide prescribing information, 2005

Amylin Analog

	Pramlintide (Symlin)
Indication	**Type 1:** as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy **Type 2:** with or without a concurrent sulfonylurea agent and/or metformin
Dose	**Type 1:** • Start at 15 µg and titrated at 15 µg increments • Maintenance dose of 30 µg or 60 µg **Type 2:** • Start at 60 µg and increased to a dose of 120 µg as tolerated *Immediately prior to each major meal (≥250 kcal or containing ≥30 g of carbohydrate*

Pramlintide prescribing information, 2005

Amylin Analog

	Pramlintide (Symlin)
Adverse Reactions (> 5%)	○Nausea, Headache ○Anorexia, Vomiting, Abdominal Pain ○Fatigue, Dizziness ○Coughing ○Pharyngitis
Comments	○Should not be used with other drugs that alter GI motility or gastric emptying ○Potential to delay absorption of concomitant oral medications ○If rapid onset is required (analgesics), consider 1 hour pre- or 2 hours post-SYMLIN dose

Pramlintide prescribing information, 2005

Amylin Analog

	Pramlintide (Symlin)
Advantages	○Weight loss ○Reduces glucose fluctuations ○Decreases insulin requirement • REDUCE prandial insulin by 50%
Disadvantages	○Injection only ○Multiple daily dosing ○Dose conversion (mcg to units) • Error potential

Pramlintide prescribing information, 2005

Amylin Analog: Administration

- Abdomen or thigh
- Do not mix with insulin
- U-100 insulin syringe
- Before each major meal
  - snack ≥250 kcal or ≥30 g CHO

Dose	Units
15 mcg	2½
30 mcg	5
45 mcg	7½
60 mcg	10
120 mcg	20 U

Sig: Inject 10 units (60 mcg) with each major meal

Pramlintide prescribing information, 2005

PLACE IN THERAPY

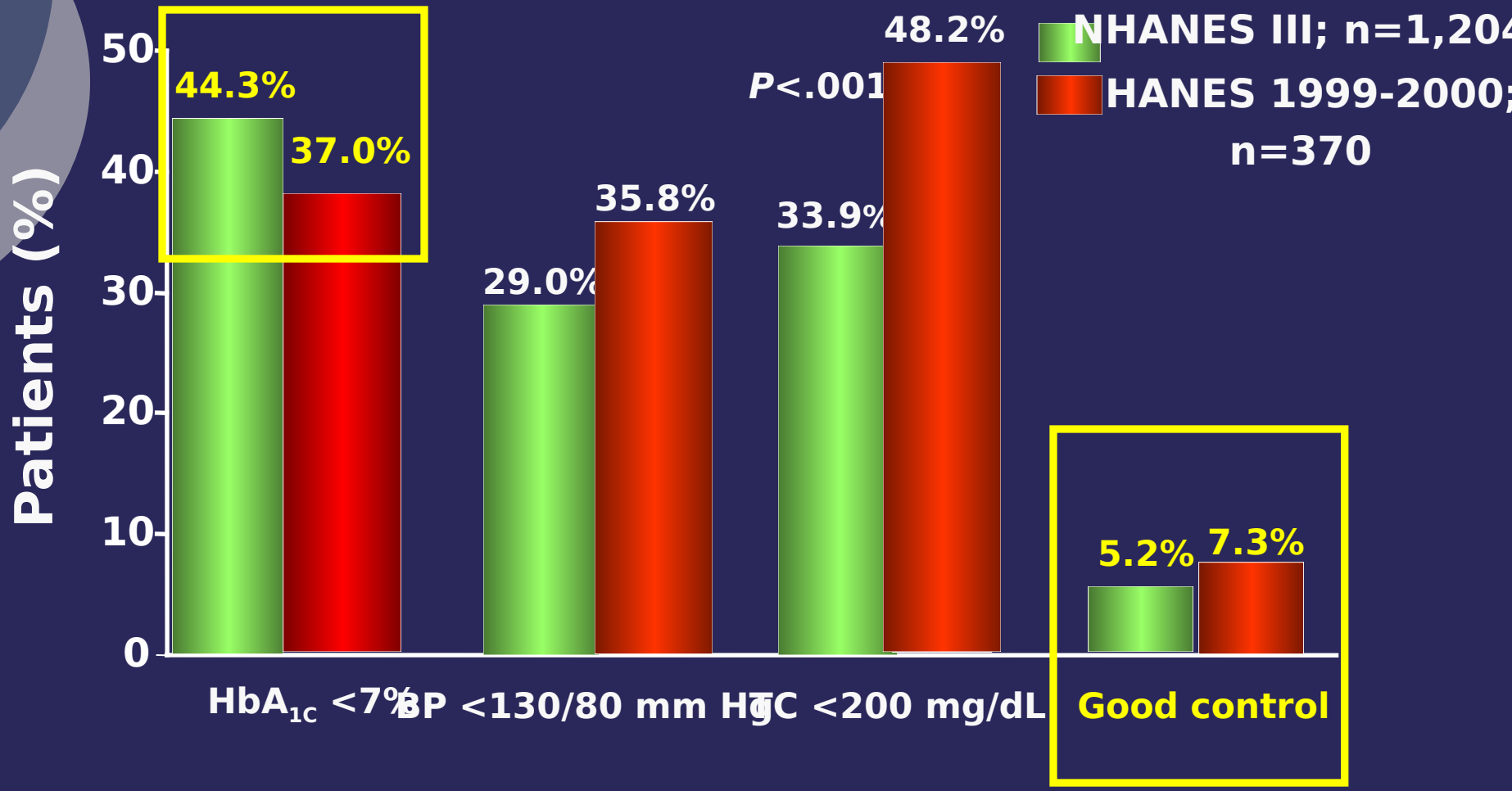
Comparative efficacy

Agent	↓ A1C (%)	Advantages	Disadvantages
Metformin	0.8 – 2.0	Low cost, weight neutral	Gi side effects
Sulfonylurea	0.9 – 2.5	Low cost	Weight, hypoglycemia
Meglitinides	0.6 – 1.9	Short duration	Short duration
TZDs	1.1 – 1.6	Improved lipid profile	Fluid retention, weight
α-glucosidase Inhibitors	0.4 – 1.3	Weight neutral	GI side effects, multi-dosing
DPP-4	0.6 – 0.8 (-1.4*)	Weight neutral, minimal hypoglycemia	cost
Exenatide	0.5 – 1.0	Weight loss	GI side effects, Injection, cost
Pramlintide	0.5 – 1.0	Weight loss	GI side effects, Injection, cost

Inzucchi SE. *JAMA* 2002. Luna B et al. *Am Fam Physician* 2001. Sitagliptin, exenatide, pramlintide prescribing

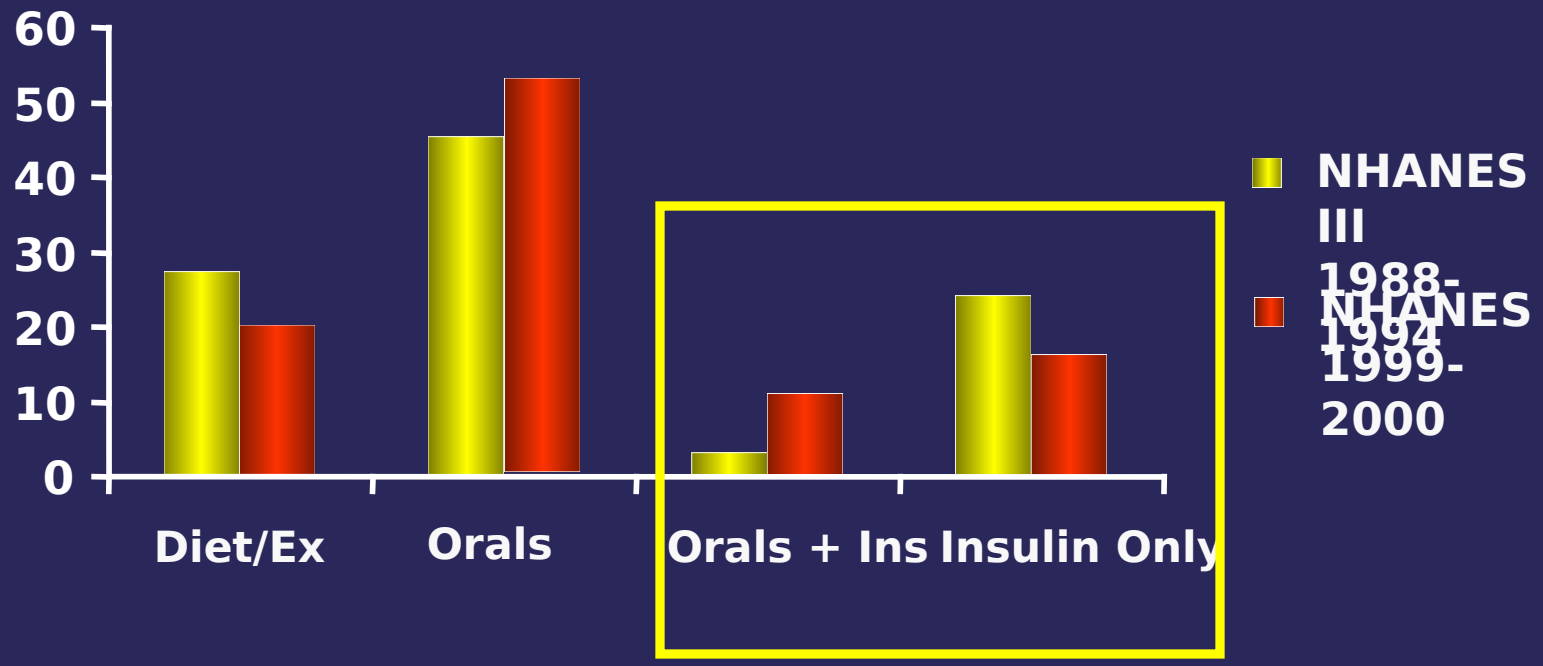
New agents: do they help?

Risk Factor Control in Adults With Diabetes: NHANES III (1988-1994)/NHANES 1999-2000



Saydah SH et al. *JAMA*. 2004;291:335-342.

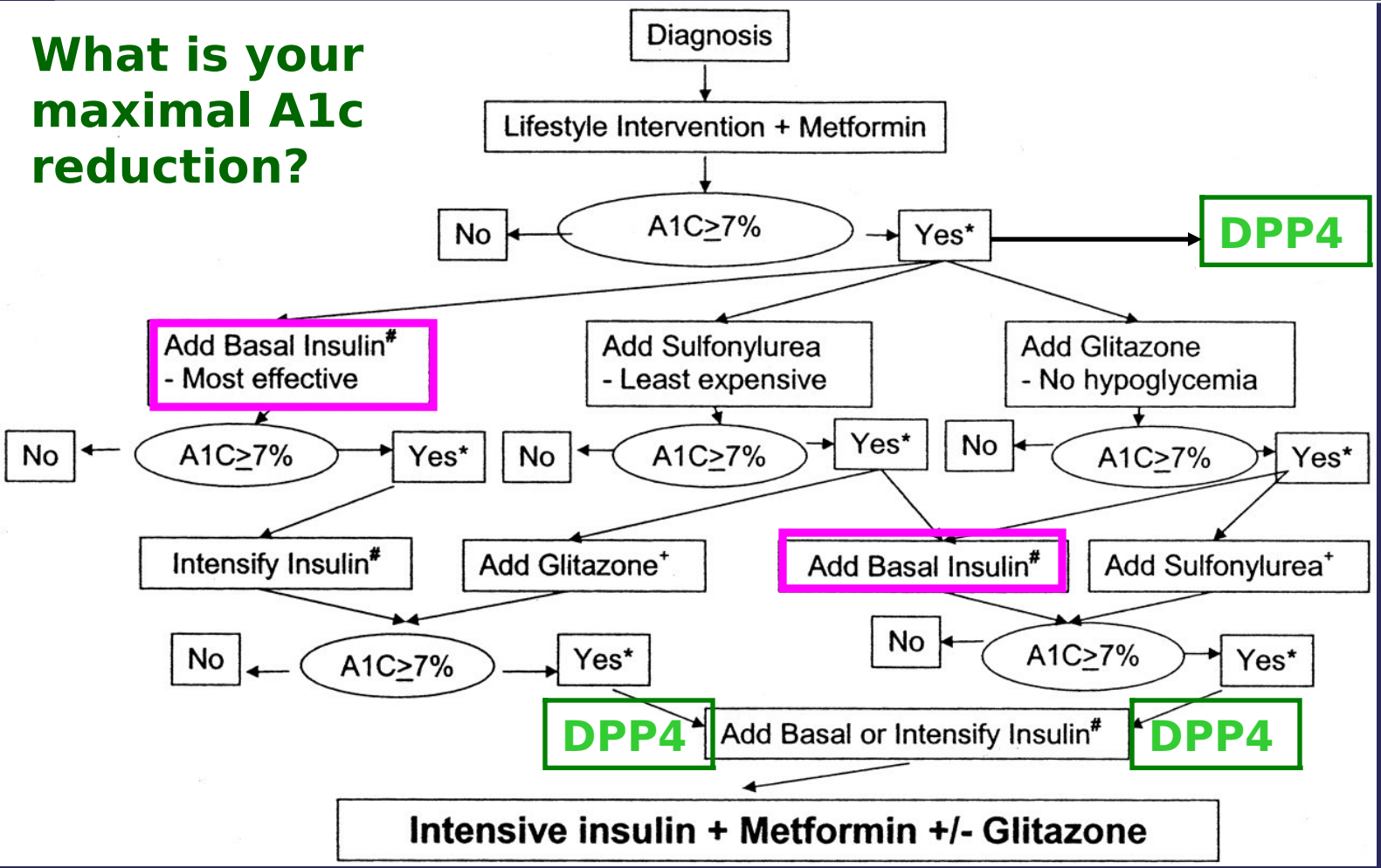
Insulin Use Remains Constant
NHANES III vs NHANES 1999-2000



Koro et al, Diabetes Care. 2004; 27(1):17-20

Treatment Algorithm

What is your maximal A1c reduction?



Standards of Medical Care in Diabetes. Diabetes Care 30:S4-S41, 2007

FDA Approval Process

- New drug to market
  1. Phase 1, 2 and 3 studies
  2. NDA submitted: marketing consideration
  3. FDA review team is assigned to evaluate drug safety and effectiveness
     - Independent Drug Safety Oversight Board (DSOB)
- Add indication (drug already on market)
  1. Supplemental NDA: add indication

The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective. http://www.fda.gov/fdac/special/testtubetopatient/drugreview.html (accessed 2007 June 6)

Adding FDA Indication

- Zinman et al.
  - Exenatide with TZD
  - Randomized control trial (16 weeks)
  - Safety and efficacy
  - N = 233
  - Mean A1c reduction (-1.0)
  - Mean weight reduction (-1.5kg)

Zinman B et al. Ann Intern Med. 2007 Apr 3;146(7):477-85

Malozowski S. Editoral. Ann Intern Med. 2007 Apr 3;146(7):527-8

Adequate trials?

- Malozowski S. Editoral.
  - Does trial fit most patients?
  - Not on maximal therapy
    - 21% not on metformin
  - No comment on education or diet
  - 29% exenatide patients dropped out
    - No subgroup analysis
- Need equal focus on outcomes and side effects

Zinman B et al. Ann Intern Med. 2007 Apr 3;146(7):477-85

Malozowski S. Editoral. Ann Intern Med. 2007 Apr 3;146(7):527-8

CDER Freedom of Information

Handbook for Requesting Information and Records from FDA

- Advisory Committees
- Disqualified/Restricted/Assurance List for Clinical Investigators
- Division of Drug Marketing, Advertising and Communications Correspondence
- Drug Approval Packages (Drugs@FDA)
- Investigational Human Drugs: Clinical Investigator Inspection List
- Special Interest Topics
- Warning Letters (FDA Freedom of Information Office)

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Conclusion

- Incretin and amylin medications can be useful in patient with diabetes
- Will you reach A1c goal with the medication you choose?
- Don’t forget insulin therapy
- Be familiar with the control trials

Questions